East African Scholars Journal of Medicine and Surgery
Abbreviated Key Title: EAS J Med Surg
ISSN: 2663-1857 (Print) & ISSN: 2663-7332 (Online)
Published By East African Scholars Publisher, Kenya

OPEN ACCESS

Volume-6 | Issue-4 | Apr-2024 | DOI: 10.36349/easjms.2024.v06i04.005

Case Report

Clinical and Biological Lupus Induced by Infliximab in Crohn's Disease

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Article History
Received: 01.02.2024
Accepted: 10.03.2024
Published: 22.04.2024

Journal homepage:
https://www.easpublisher.com

Quick Response Code

Abstract: The use of anti-TNFs in Crohn's disease (CD) is often associated with the appearance of antinuclear antibodies, and more rarely with anti-native DNA antibodies. Anti-TNF-induced lupus remains exceptional. We report the case of a 52-year-old woman, followed for colonic Crohn's disease, treated with Infliximab. After 12 months of treatment with anti-TNF alpha (Infliximab), the patient developed clinical and biological lupus with positive antinuclear antibodies (ANA) and anti-native DNA antibodies (IgG). Infliximab treatment was discontinued. Six months after stopping the treatment, the patient had no recurrence of clinical signs, and immunological examinations showed a marked decrease in total ANA and anti-native DNA antibodies (IgG).

Keywords: Crohn's Disease, Cutaneous Lupus, Joint Lupus, Immunological Assessment, Anti-TNF Alpha, Infliximab.

INTRODUCTION

Infliximab, an anti-tumor necrosis factor alpha (anti-TNF-α) antibody, has been approved for its effectiveness for more than 15 years in chronic inflammatory bowel diseases (IBD), inflammatory rheumatism (rheumatoid arthritis, spondyloarthritis), and psoriasis. The effectiveness of anti-TNFs is indisputable, even though the arrival of new biopharmaceuticals with other therapeutic targets has further improved the management of these conditions. The side effects of anti-TNFs are well known, including the risk of severe infection and reactivation of latent tuberculosis. Beyond the frequent side effects, there are also rarer side effects, including autoimmune manifestations induced by anti-TNFs. These remain infrequent but must be considered in the presence of unusual clinical manifestations, particularly joint or cutaneous. Drug-induced lupus is the main autoimmune complication of anti-TNFs, but cases of alopecia, hepatitis, demyelination, ophthalmological autoimmune disorders, or autoimmune cytopenias have also been reported. We report a case of a patient followed in our department for Crohn's disease who developed clinical and biological lupus under Infliximab.

CASE REPORT

A 52-year-old woman, with no particular medical history, followed for colonic Crohn's disease of inflammatory phenotype classified A3L2B1p according to the Montreal classification with anal-perineal lesions classified U0F1aS0 according to the Cardiff classification, was treated with Infliximab up to S46. After 12 months of treatment with anti-TNF alpha (Infliximab), the patient presented with asthenia, rash during sun exposure (photosensitivity), associated with very marked axial and peripheral inflammatory joint pain. The clinical examination was unremarkable. Biological examinations showed an inflammatory hypochromic microcytic anemia with (Hb: 9.7 g/dl; Ferritin: 150), an inflammatory syndrome with a C-reactive protein at 56 mg/l (N < 5 mg/l) and an erythrocyte sedimentation rate at 44 mm at the first hour. Infectious and tuberculous workups were negative, antinuclear antibodies (ANA) were positive at 320, anti-native DNA antibodies (IgG) were 92.3 IU (normal <40), and anticardiolipins were negative. X-rays of the limbs and an MRI of the cervico-dorso-lumbo-sacral spine were unremarkable, with no sacroiliitis. Infliximab treatment was discontinued. Photosensitivity, inflammatory joint pain, and inflammatory syndrome improved spontaneously in less than 4 weeks. Six months after stopping the treatment, the patient had no recurrence of cutaneous or joint signs, and immunological examinations showed a marked decrease in total ANA and anti-native DNA antibodies (IgG).

DISCUSSION

Infliximab is a chimeric monoclonal antibody with high affinity and specificity for tumor necrosis factor alpha (TNF-α). TNF-α plays a crucial role in the development and maintenance of chronic autoimmune inflammatory diseases (IMID) designated by IMID

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(Immune Mediated Inflammatory Diseases). In the 1990s, TNF-α was identified as a cytokine playing an important role in Crohn's disease, but it can also lead to immunogenicity and autoimmunity. Human cells (which account for about 75% of the molecule) and mouse cells (25%) are used for its synthesis, resulting in a so-called "chimeric" antibody. Infliximab belongs to the family of anti-TNF treatments, such as adalimumab. When infliximab is infused, it remains in the body for 2 to 3 months before being destroyed.

During Inflammatory Bowel Diseases (IBD), this treatment has demonstrated its effectiveness in several studies comparing it to placebo (inactive medication). It obtained first marketing authorization (MA) in Crohn's disease in Europe as early as 1999. Since then, this MA has been progressively extended to other diseases (ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriasis).

Immediate intolerances to intravenous infliximab infusions have been reported in 3% to 6% of cases from the first clinical trials ATTRACT and ACCENT I, in rheumatoid arthritis, and in Crohn's disease. They were most often moderate, such as skin rashes or itching, but 0.3% to 1% of patients had more severe reactions (laryngeal edema, bronchospasm). These immediate effects, related to the presence of specific anti-infliximab antibodies, are attenuated by the combination with immunosuppressive treatments, such as Azathioprine and Methotrexate. Some isolated cases of late skin reactions (eczema, psoriasis, vasculitis, or skin infections) have also been reported.

Anti-TNFs also induce the appearance of autoantibodies. TNFα inhibition would lead to a T lymphocyte imbalance in favor of Th2 cytokine production (interleukins 4 and 10), implicated in the occurrence of anti-native DNA antibodies and induced lupus. In IBDs, in a cohort of 180 patients on anti-TNF, 44.4% had positive ANA and 15.6% had anti-native DNA antibodies. In another study of Crohn's disease on infliximab, ANA and anti-DNA were induced in 53% and 35% of cases, respectively. In contrast, no other autoantibodies were found (anti-cardiolipin, anti-tissue, anti-thyroid, anti-CCP, rheumatoid factor). However, the occurrence of induced lupus is rare in less than 1% of patients. It can be chronic cutaneous lupus, subacute lupus, or acute disseminated lupus.

The most frequently implicated anti-TNFs are infliximab and etanercept. Symptoms can appear from 1 to 48 months after the start of treatment. The clinical presentation begins with general signs such as general deterioration, fever, and weight loss. Musculoskeletal signs such as myalgia and inflammatory arthralgia are present in 50 to 90% of cases. Skin involvement is common and affects 25 to 50% of patients and may include photosensitivity, purpura, erythema nodosum, and malar rash. Pleuro-pulmonary and cardiac involvement is possible but remains rare, including pleurisy and rarely pericarditis. Digestive involvement such as hepatomegaly and splenomegaly may exist. Neuropsychiatric and renal manifestations such as glomerulonephritis are exceptional in induced lupus. Biological abnormalities are rare and nonspecific. Autoimmune manifestations induced by anti-TNFs are a rare complication of these biopharmaceuticals. Most often, it is the induction of lupus-like autoimmunity characterized by the appearance of ANA and anti-native DNA antibodies, found respectively in 20-60% and 15-30% of patients on anti-TNFs.

The diagnosis of induced lupus involves discontinuation of the inducing treatment, especially in the presence of visceral or renal involvement. The favorable evolution of clinical and biological signs (decrease in ANA and anti-native DNA antibodies) observed shortly after stopping infliximab remains an element in favor of the diagnosis.

The reintroduction of another anti-TNF-alpha is discussed in the literature and must take into account the benefit/risk balance for each patient. In the study by Williams *et al.*, ten patients who developed lupus under anti-TNF-alpha continued their immunosuppressive treatment after switching to another anti-TNF-alpha without recurrence of lupus symptoms.

CONCLUSION

Infliximab plays an important role in the management strategy of chronic inflammatory bowel diseases (IBD), but it can also lead to lupus autoimmunity. This observation, which adds to the other cases recently reported in the literature, supports the possibility of induced lupus under infliximab.

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Cite This Article: D. Rajih, H. ELmarmouk, F. Z. Lairani, O. Nacir, A. AitErrami, S. Oubaha, Z. Samlani, K. Krati (2024). Clinical and Biological Lupus Induced by Infliximab in Crohn's Disease. *East African Scholars J Med Surg, 6*(4), 142-144.